REMARKS

Status of Claims

Claims 1-21, 23-27, and 29-80 are currently pending. Claims 11-14, 24, 29, 32-34, 50, and 54-62 are withdrawn. Claims 77-80 are added. Support for claims 77-80 can be found, for example, in Figure 1 of the instant application. Accordingly, Applicants submit that no new matter is introduced into the specification by way of the present amendments pursuant to 35 U.S.C. § 132. Applicants respectfully request entry of the amendments, reconsideration of the rejections, and allowance of the pending claims.

Reply to Claim Rejections under 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 1-6, 15-21, 23, 25-27, 30-31, 35-49, 51-53, and 63-67 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Pickar *et al.* U.S. Patent No. 5,492,907 ("Pickar") in view of Beasley, Jr. *et al.* U.S. Patent No. 5,605,897 ("Beasley"). The Examiner argued that arguments previously put forth by Applicants were unpersuasive. The Examiner argued, on pages 9-10 of the Office Action, that Pickar *et al.* teaches a combination of an α_2-adrenergic receptor antagonist and a D_2 dopamine receptor antagonist, although it does not teach an atypical antipsychotic drug. Beasley, Jr. *et al.* teaches olanzapine as an antagonist of dopamine at D_1 and D_2 receptors. The Examiner reasons that because Pickar *et al.* teaches the combination of α_2-adrenergic receptor antagonist and a D_2 dopamine receptor antagonist and that Beasley, Jr. *et al.* teaches that olanzapine is a D_2 dopamine receptor antagonist that the combination of an α_2-adrenergic receptor antagonist with an atypical antipsychotic neuroleptic like olanzapine would have been obvious to one of ordinary skill in the art. Further, Beasley, Jr. *et al.* teaches that olanzapine may be used to treat schizophrenia, a serious psychotic mental illness.

Applicants respectfully traverse the Examiner's maintained rejections. First Applicants submit, supported by the Declaration under 37 C.F.R. § 1.132 by David Pickar, that one of ordinary skill in the art would not have a reasonable expectation of success for the invention of a method of treating a serious psychotic mental illness by

administering a combination of an α_2-adrenergic receptor antagonist and an atypical antipsychotic neuroleptic to a patient in need of such treatment in light of the teachings of Pickar and Beasley. Second, Applicants submit that the Examiner has neglected to consider the evidence of unexpected properties Applicants described in their previous response.

No Reasonable Expectation of Success

Applicants submit, supported by the Declaration under 37 C.F.R. § 1.132 by David Pickar, that one of ordinary skill in the art would not have a reasonable expectation of success for the invention of a method of treating a serious psychotic mental illness by administering a combination of an α_2-adrenergic receptor antagonist and an atypical antipsychotic neuroleptic to a patient in need of such treatment in light of the teachings of Pickar and Beasley. Applicants submit, supported by the Declaration of David Pickar that Pickar does not teach the treatment of a serious psychotic mental illness with a combination of an α_2- adrenergic receptor antagonist with an atypical antipsychotic. Pickar teaches the combination of an α_2-adrenergic receptor antagonist and a D_2 receptor antagonist for the treatment of a serious psychotic mental illness.[1] Pickar explains that drugs with a mechanism of action of D_2 antagonism (D_2 antagonists or D_2 blockers) are known as conventional or "typical antipsychotics"[2] and that a "significant" number of patients have proven resistant to treatment with such "typical antipsychotic" drugs.[3] The unexpected finding described in Pickar is that the addition of an α_2- adrenergic receptor antagonist to a "typical antipsychotic" (*i.e.*, the D_2 blocker, fluphenazine)[4] resulted in improvement beyond the response to the "typical antipsychotic" (D_2 blocker) alone.[5] Pickar does not teach the combination of an α_2-adrenergic receptor antagonist added to "atypical antipsychotic" drugs such as olanzapine with mechanisms of action including both D_2 blocking effects and antagonism of the 5-HT-2 receptor. Thus, Applicants

[1] *See* Pickar at the Abstract.
[2] *Id.* at column 1; lines 10-14.
[3] *Id.* at column 1; lines 18-35.
[4] *Id.* at column 4; lines 20-30.
[5] *Id.* at Figure 1.

submit that one of ordinary skill in the art would not equate D_2 blockers with D_2/5HT-2 blockers (serotonin – dopamine antagonists)[6] as the Examiner reasons.

Applicants further submit that Beasley does not remedy the deficiencies of Pickar. Beasley does not suggest the replacement of the typical antipsychotic of Pickar with an atypical antipsychotic. Beasley teaches, as is well known in the art, that olanzapine "shows its greatest activity at the 5-HT-2 receptor."[7] It is widely known that the mechanism of action of olanzapine and other "atypical antipsychotics" with disorders of the central nervous system is through antagonism of the 5-HT-2 receptor in conjunction with antagonism of the D_2 receptor.[8]

One of ordinary skill in the art would not have expected atypical antipsychotics, like olanzapine to be effective in combination with an α_2-adrenergic receptor antagonist, let alone have improved function as is demonstrated in the above-referenced patent application based on the teachings of Pickar and Beasley and the knowledge of one of ordinary skill in the art. It is well known in the art that atypical psychotics have their greatest activity at the 5-HT-2 receptor and not at the D_2 receptor.[9] This difference in D_2 receptor occupancy between typical and atypical antipsychotics has clinical relevance. For example, when D_2 occupancy exceeds a threshold in the range of 75%-80% of D_2 receptor occupancy, extrapyramidal symptoms can result.[10] Atypical antipsychotics have lower D_2 occupancy than this threshold.[11] For example, clozapine has 20%-67%.[12] Moreover, atypical antipsychotics (or second generation antipsychotics) have different clinical effects from typical antipsychotics (or first generation antipsychotics) in patients

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[6] *See* Kapur S, Remington G. Serotonin –dopamine interaction and its relevance to schizophrenia. American Journal of Psychiatry 1996; 153:466-476; Meltzer HY, *et al.* Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2, and serotonin-2 PK values. J Pharmacol Exp Therapeutics (1989) 251:238-246; Physician Desk Reference, 2007 – label for Zyprexa, p 1830 Under the heading for clinical pharmacology; Stockmeier CA *et al.* Characterization of typical and atypical antipsychotic drugs based on in vivo occupancy of serotonin and dopamine receptors. J Pharmacol Exp Therapeutics 1993;266:1374-1384; and Davis *et al.* A meta-analysis of the efficacy of second-generation antipsychotics. Arch. Gen. Psychiatry 60:553-564 (June 2003). attached as Exhibits 1-5, herewith.

[7] *See* Beasley at column 12, lines 37-42.

[8] *See* Exhibits 1-4, filed herewith and and Beasley at column 12, lines 33-42.

[9] *See* Exhibit 2 at the Abstract, page 242, first four lines of paragraph bridging columns 1 and 2, and Exhibit 3 at the Abstract, page 1374, first 3 lines of column 2, page 1377 Table 1, page 1378, first 6 lines of the Discussion, page 1380, first four lines of paragraph bridging columns 1 and 2, and page 1382, column 2, lines 9-13.

[10] *See* Exhibit 1 at page 470, first paragraph in "Extrapyramidal Symptoms" section.

[11] *Id.*

[12] *Id.*

with schizophrenia.[13] Thus, one of ordinary skill in the art would know that there are significant differences in the mechanism of typical and atypical antipsychotics and that these differences has clinical relevance.

The results shown in the present application are unexpected in light of the teachings of Pickar and Beasley. Beasley teaches that olanzapine inhibited conditioned avoidance response in rats in the dose range of 4-7 mg/kg.[14] Conditioned avoidance response is a standard behavioral test predictive of antipsychotic activity. One of ordinary skill in the art would not have expected that the addition of the α_2-adrenergic receptor antagonist idazoxan to olanzapine would reduce the dose required for inhibition of conditioned avoidance response to 2.5 mg/kg as shown in the above-referenced patent application. This is because of the mechanical and clinical differences between typical and atypical antipsychotics described above. This unexpected finding, neither predicted nor contemplated by Beasley or Pickar, has direct implications for antipsychotic therapeutics, including enhanced efficacy and dosage reduction, as shown in the present application.

Unexpected Properties

Applicants submit that the Examiner did not consider the unexpected properties submitted in the previous response by Applicants when the Examiner maintained the rejection of claims 1-6, 15-21, 23, 25-27, 30-31, 35-49, 51-53, and 63-67 under 35 U.S.C. § 103(a). Evidence of unexpected results must be weighed against evidence supporting prima facie obviousness in making a final determination of the obviousness of the claimed invention.[15] The present application discloses the unexpected results that an atypical antipsychotic drug, olanzapine, combined with an α_2-adrenergic receptor antagonist without undesirable side effects and superior efficacy.[16] As set forth in KSR Int'l Co. v. Teleflex Inc., "combining elements that work together 'in an unexpected and fruitful manner' would not have been obvious." 127 S. Ct. 1727, 1740 (2007). The present claims are directed to the combination of an atypical antipsychotic drug with an

[13] *See* Exhibit 5 at the Background and page 553 column 1.
[14] *See* Beasley at column 11, lines 11-27.
[15] MPEP § 716.02(c).
[16] *See* pages 23-26 and Figure 1 of the instant specification.

α_2-adrenergic receptor antagonist produces both an unexpected and fruitful result. Example 1 of the specification shows that adjunctive treatment with a selective α_2 adrenergic receptor antagonist (idazoxan) to relatively low doses of an atypical antipsychotic with low affinity for α_2 adrenergic receptors (olanzapine) produced a significant antipsychotic-like effect without catalepsy. The present results, obtained by a combination of idazoxan and olanzapine, demonstrate an equally or more effective suppression of the CAR by the use of only 2.5 mg/kg of olanzapine. Thus, these data indicate that the dose of olanzapine required to obtain an effective antipsychotic effect may be reduced by almost 50% through the adjunct treatment with idazoxan. These results are truly unexpected as explained above.

In light of the teachings of Pickar and Beasley these results are unexpected. Pickar teaches only that atypical neuroleptics are not effective because of their side effects.[17] Beasley teaches that olanzapine is a compound with D-1 and D-2 dopamine receptor antagonism, and well as antagonistic of norandrenergic α receptors.[18] Beasley also teaches that olanzapine is effective in the treatment of schizophrenia, even at low doses, when used in monotherapy.[19] Neither Pickar nor Beasley teach the combination of olanzapine with any other drug, let alone idazoxan. Moreover, neither teach the statistically significant results shown in Example 1 and Figure 1 of the instant specification showing a synergistic improvement in avoidance of side effects with the combination of idazoxan with olanzapine over olanzapine alone, particularly when olanzapine is administered at 2.5 mg/kg. This was done without cataleptic side effects. These results are unexpected in light of the teachings of Pickar and Beasley and should be taken as evidence that the invention of claims 1-6, 15-21, 23, 25-27, 30-31, 35-49, 51-53, and 63-67 is non-obvious over the teachings of Pickar and Beasley.

Reply to Double Patenting Rejection over U.S. Patent No. 5,492,907

Claims 1, 2, 3, 5, and 6 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 5 of Pickar in view of

[17] *See* Pickar *et al.* at column 1, lines 36-40.
[18] *See* Beasley Jr. *et al.* at column 2, lines 55-60.
[19] *Id.* at column 7, lines 9-44.

Beasley. Obviousness-type double patenting requires rejection of an application claim when the claimed subject matter is **not patentably distinct** from the subject matter claimed in a commonly owned patent. See MPEP § 804(II)(B)(1)(emphasis in original). Further, a double patenting rejection of the obviousness-type, is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" except that the patent principally underlying the double patenting rejection is not considered prior art. MPEP § 804(II)(B)(1), citing *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967).

This rejection sets forth the same rationale for combining these references as was set forth in the 35 U.S.C. § 103(a) rejection. As presented above, however, Applicants respectfully submit that the unexpected properties of the claimed invention render the subject matter of claims 1-3 and 5 of Pickar in light of the teachings of Beasley, non-obvious. Further, the claims of the present application are patentably distinct from the claims of Pickar. Accordingly, Applicants respectfully request withdrawal of this rejection.

Reply to Double Patenting Rejection over U.S. Patent No. 5,663,167

Claims 1, 2, 3, 5, and 6 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6 and 7 of Pickar *et al.* (U.S. Patent No. 5,663,167) in view of Beasley. U.S. Patent No. 5,663,167 is related to U.S. Patent No. 5,492,907 (Pickar) cited in the above double patenting rejection. As with U.S. Patent No. 5,492,907, U.S. Patent No. 5,663,167 discloses the combination a typical antipsychotic drug with an α_2-adrenergic receptor antagonist. In combining U.S. Patent No. 5,663,167 with Beasley, the Office Action uses the same rationale for combining these references as was set forth in the 35 U.S.C. § 103(a) rejection combining U.S. Patent No. 5,663,167 with Beasley. As presented above, however, Applicants respectfully submit the lack of reasonable expectation of success and unexpected properties of the claimed invention render the subject matter of claims 1-4, 6 and 7 of U.S. Patent No. 5,663,167 in light of the teachings of Beasley, non-obvious. Further, the claims of the present application are patentably distinct from the claims of U.S. Patent No. 5,663,167. Accordingly, Applicants respectfully request withdrawal of this rejection.

Allowable Subject Matter

While the Examiner listed claims 68-71 as rejected on page 1 of the Office Action, no specific reasoning was given for rejection of these claims and these claims were not listed as rejected elsewhere in the Office Action. Previously, claims 68-71 were rejected under 35 U.S.C. § 112, first paragraph, but the Examiner withdrew this rejection on page 2 of the Office Action. Further, claim 68 is an independent claim and so would not be considered rejected for depending from a claim subject to a rejection mentioned in the Office Action. Claims 69-71 are pending, not rejected and depend from claim 68, which Applicants submit is an allowable claim. Thus, Applicants submit that claims 68-71 are in condition for allowance.

Also, claims 72-76 are pending in the instant application and are not marked withdrawn or rejected on page 2 of the Office Action. However, on page 3 of the Office Action, the Examiner does not mention these claims as being acted on the merits. Applicants request clarification of the status of claims 72-76.

CONCLUSION

An indication of allowance of all claims is respectfully solicited. Early notification of a favorable consideration is respectfully requested. In the event any issues remain, Applicant would appreciate the courtesy of a telephone call to their counsel to resolve such issues and place all claims in condition for allowance.

Respectfully submitted,

Dated: May 28, 2008 By: /Sean M. Coughlin/

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